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EXAMINER	
GOLLAMUDI, SHARMILA S	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 11/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/885,287	SEWING ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-8,10-19,21 and 23-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-8,10-19,21 and 23-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt Amendments/Remarks and IDS filed 8/30/06 is acknowledged. Claims **1, 3-8, 10-19, 21, and 23-27** are pending in this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 10-19, 21, and 23-25, 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 has been amended to recite "wherein the mineralized collagen matrix is constructed in the form of layers, whereby at least one of said layers comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate *clusters* and crystalline hydroxyapatite." Amorphous calcium phosphate clusters does not have support in the specification as pointed out in the previous office action. Applicant cites page 12, lines 10-17 for support. The examiner notes on page 10, the applicant teaches spherical calcium phosphate clusters. However, this does not provides support for amorphous calcium phosphate clusters. Further, the recitation "at least one layer comprises a composite of mineralized collagen fibrils, amorphous calcium phosphate *clusters* and crystalline hydroxyapatite" implies that the device may comprise more than one layer comprising a combination of mineralized collagen fibrils,

amorphous calcium phosphate *clusters* and crystalline hydroxyapatite does not have support. Applicant cites page 12, lines 10-17 for support. However, the examiner notes that page 12 only provides support for one layer comprising a combination of amorphous calcium phosphate, hydroxyapatite, and collagen.

Response to Arguments

Applicant's arguments filed 8/30/06 have been fully considered but they are not persuasive. Applicant argues that the instant amendments overcome the new matter issue; however the claims still recite amorphous calcium phosphate *clusters*, which is considered new matter as set forth in the last office action. Applicant has not addressed this nor has applicant cited support for the limitation. Further, the amendment does not overcome the new matter rejection since applicant is still attempting to claim more than one layer comprising a combination of collagen fibrils, amorphous calcium phosphate *clusters* and crystalline hydroxyapatite, which does not have support. The examiner notes page 12 only provides support for one layer comprising a combination amorphous calcium phosphate, hydroxyapatite, and collagen, not multiple layers.

The rejection of claims 2-3 and 23 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments of 8/30/06.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 1, 3-8, 10-19, 23, and 27 under 35 U.S.C. 103(a) as being unpatentable over Rhee et al (5,543,441) is withdrawn since Rhee does not teach the use of amorphous calcium phosphate.

Claims 1, 4, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in further view of Lussi et al (5,167,961).

JP teaches a prosthetic implant coated with hydroxyapatite (HA). The implants provide an implant that is close to osseous tissue and such implants fully "unit with existing osseous tissue and will promote growth of the new bone". [002]. The coating contains highly crystalline hydroxyapatite and low content of amorphous calcium phosphate. See abstract. The examples teaches coating a titanium-alloy implant. The coating also has a low content of tricalcium phosphate and doped with carbonate. See examples and [0080].

JP does not teach the particle size of HA or collagen.

Constantz teaches a hydroxyapatite prosthesis coating which allows for ingrowth of natural bone. See abstract. Constantz teaches the use of other ions and components to modify the

HA composition such as using fluoride, carbonate, hydrogen, etc, which influence the dissolution behavior of the coating. see column 2, lines 50-60. Constantz teaches the coating composition may further comprises collagen and growth factors to enhance bony ingrowth. See column 6, lines 1-10. The composition is coated on a steel or titanium. See column 6, lines 14-20. The crystals have a diameter of 0.01microns (10nm) to 20 microns (20000nm) (see column 2, line 60) and a length of 0.01 microns (10nm) to about 10 microns (10000nm) (see column 3, line 40). Constantz teaches a firstly layer of the coating with a thickness of 0.01microns (10nm) to 20 microns (20000nm). See column 3, lines 39-41.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatite-like crystallites with a particular degree of crystallinity, habit and size (irregular platelike morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4,

lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20.

Firstly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of JP and Constantz et al and further add collagen to the hydroxyapatite coating. One would have been motivated to do so since Constantz teaches a HA coating composition that may further comprise collagen and growth factors to enhance bone growth. A skilled artisan would have reasonably expected similar results since both references are in the same filed of endeavor, i.e. implants coated with hydroxyapatite compositions. With regard to claim 4, a skilled artisan would have been motivated to add other ions such as fluoride or carbonate to manipulate the resorption rate of the coating. Further, Constantz teaches various particles sizes of HA that are suitable for HA coating compositions.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of JP and Lussi et al and specifically utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would

have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster. A skilled artisan would have reasonably expected similar results since JP teaches the purpose of the hydroxyapatite coating on implants since to provide a surface for bone ingrowth and to mimic natural bone.

Note that the recitation "wherein the coating is obtained by precipitating phosphate from a solution in the presence of collagen" and process limitation in claims 11-19 and 27 are product-by-process limitation. According to MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, collagen in combination with mineral components implicitly tends to separate into phases or layers. Note US 5,543,441, column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

Claims 5-6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) in further view Sauk et al (4,780,450).

The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III.

Sauk et al teach a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). Sauk teaches the collagen provides a structural matrix

preventing migration of the calcium particles and the calcium phosphate particles also interact with the collagen to improve the physical properties of the collagen matrix by reducing its compressibility and increasing its mechanical strength. Sauk teaches not only does the combination provide a scaffold for new bone ingrowth but it mimics natural bone. A mixture of type I and type III collagen is taught (example 1). Sauk et al teach in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of above references and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

Claims 7 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) in further view of Geistlich et al (5,573,771).

The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not teach the use of gelatin.

Geistlich teaches a bone mineral product that comprises collagen (Type I or Type I-III), gelatin, and calcium phosphate components. The reference teaches gelatin provides strength and freedom from antigencity. See column 2, lines 20-30. Further, the reference teaches the use of active agents such as growth factors, antibiotics, etc to allow the bone to be used as a drug carrier. See column 3, lines 20-65.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references and further add gelatin to JP's coating composition. One would have been motivated to do so since Geistlich teaches gelatin not only adds strength to bone mineral products but it also reduces an adverse immune response.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over JP 11-047259 in view of Constantz et al (5,279,831) optionally in view of Lussi et al (5,167,961) in further view of Liu (6,300,315).

The teachings of JP, Constantz, and Lussi, have been set forth above.

The references do not teach the use of additional calcium phosphates as claimed in claim 3.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be

replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the above references and Liu and further add the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including tricalcium phosphate, hydroxyapatite, amorphous calcium phosphate, octacalcium phosphate to provide a strong and flexible membrane. Further, JP teaches the coating has a small weight percent of tricalcium phosphate; thus if a skilled artisan desired to utilize octacalcium phosphate in place of tricalcium phosphate, a skilled artisan would have been motivated to substitute accordingly in view of Liu's teaching that the mineral phase may be made of a mixture of calcium phosphates.

Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961).

Worch et al disclose a metallic substrate (titanium) having a polyphase oxide coating. The polyphase oxide coating is produced by bringing the metallic substrate into contact with an organic and/or inorganic component to be integrated into the polyphase oxide coating such that the inorganic and/or organic phases are present at or in the direct vicinity of the substrate surface and by simultaneously or subsequently anodically polarizing the substrate material in an electrolytic solution. See abstract. The process of coating the implant yields a two-layer oxide coating, where the outer layer is the inorganic and/or the organic phase. See column 2, lines 32-

45. The inorganic component is calcium phosphate and the organic component is Type I collagen. See column 2, lines 46-60. Claim 1 envisages a combination of an organic phase and inorganic phase and claim 4 envisages calcium phosphate as the inorganic phase. Example 1 discloses a coating thickness of 250 nm (.250 micrometers) on the metallic implant. Worch discloses a process wherein the metallic implant is immersed in a collagen solution at the instant pH and temperature and then coated again with a phosphate solution. Note that the use of calcium ions in this solution is clearly envisaged as noted in column 2, lines 46-60 and claim 4.

Although Worch teaches the use of calcium phosphates as the inorganic phase, Worch does not teach specify the form of calcium phosphate or the size of the calcium phosphate. Also Worch does not teach the incorporation of components as recited in claim 4 (doping agents) or 8 (medicaments).

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at least a portion of the

phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatitelike crystallites with a particular degree of crystallinity, habit and size (irregular platelike morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal

defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20. .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Worch and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen. Further, Worch teaches the combination of calcium phosphate phases and collagen wherein it is clear that Worch contemplates utilizing more than one form of calcium phosphate. Further, on column 1, lines 45-55, Worch states the deficiency of the prior art is that it only utilizes resorbable calcium phosphate and not hydroxyapatite and thus "the complete character of the implant is lost". Thus, one would have expected success with the instant combination since Worch implicitly teaches a combination of hydroxyapatite and resorbable calcium phosphate (not crystallized calcium phosphate). With regard to the instantly claimed doping agents, it would have been obvious to dope Worch's mineralized collagen since Liu teaches the adding minor portions of fluoride or carbonate to the mineralized collagen to provide certain desired properties and to resemble or simulate biological apatite. With regard to the instantly claimed drugs, it would have been obvious to add certain drugs depending on the desired effect of the implant as taught by Liu.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Worch, Liu, and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

Note that the process limitation in claims 11-19 and 27 are product-by-process limitation. According to the MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to the layers, it is the examiner's position that collagen in combination with mineral components implicitly tends to separate into phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's position.

Response to Arguments

Applicant argues that the combination of Worch et al and Liu et al do not teach the instant particle size. Applicant argues that the claims have been amended to recite the coating is "adhered to the metallic implant which overcomes the rejection over Worch et al. Applicant argues that the coating of Worch are embedded in the oxide surface of the implant and not

deposited on the implant surface. Applicant argues that Worch describes an electrochemical coating process, which forms a two-layered system, wherein the outer layer comprises an organic and/or inorganic phase. Applicant argues that Worch does not describe the process for producing a mineralized collagen matrix.

Applicant's arguments filed 8/30/06 have been fully considered but they are not persuasive. Firstly, the examiner notes that Worch and Liu do no teach the instant particle size and thus the examiner relies on Lussi et al. Secondly, the definition of adhered is to: To stick fast by or as if by suction or glue. To cause to adhere; make stick. The examiner points out that term "adhered to" does not exclude embedding since embedding is a way of joining (sticking) two surfaces together. Worch discloses the phases are integrated by adsorption, sedimentation application, or deposition. See column 2, line 65 to column 3, line 5. Worch also discloses that the inorganic and organic phases are integrated into the oxide phase and extend beyond it. See claim 23. Additionally, Worch discloses the metallic implant is inserted into a collagen solution so that the collagen fibrillae adsorb to the surface of the implant. The examiner notes that the instant examples of the specification also immerse the implant into the collagen solution at the same pH and temperature. Moreover, the examiner notes on page 7 of the instant disclosure, applicant states that the coating the metallic implant may be done via the process disclosed in WO 98/17844. The examiner points out that US '718 is the English equivalent of WO 98/17844. Thus, the prior art and the instant invention must be "adhered" to the metallic implant in the same way. Lastly, although Worch polishes the metallic substrate with oxide (which integrates with the organic and inorganic phases), it should be noted that the claims do not exclude the oxide layer.

Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Worch et al (6,524,718) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) in further view of Sauk et al (4,780,450).

The teachings of Worch, Liu, and Lussi, have been set forth above.

The references do not specify the instant collagen combination, i.e. type I and type III.

Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a structural matrix and the salt regulates and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Worch, Liu, Lussi, and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

Response to Arguments

Applicant argues that Sauk does not teach a porous composition comprising a crystalline calcium phosphate, a calcium salt, and collagen to osseous repair. Applicant argues that Sauk does not teach the instant coating process or teach electrochemical migration and precipitation.

Applicant's arguments filed 8/30/06 have been fully considered but they are not persuasive. It appears that applicant's arguments pertain to the references individually and not the combination of references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner relies on Sauk to specifically teach the conventional use of a mixture of collagen types in collagen-calcium phosphate matrices. Applicant has not addressed the examiner's motivation and rather attacks for not teaching all of the claimed limitations. However, the combination of Worch, Liu, Lussi, and Sauk meet all the claimed limitations.

Claims 1, 3-4, 10-16, 18-19, 21, 23-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in further view of Lussi et al (5,167,961).

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared

to amorphous calcium phosphate. The calcium phosphate is selected from either tricalcium phosphate and hydroxyapatite is taught. See claims and examples. The coating matrix comprises interlocking fine particle in the range of 2-5 microns. See example 2. The micropores in the calcium phosphate compound coating also encourages better adhesion of collagen. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not teach the combination of amorphous calcium phosphate and hydroxyapatite (HA) or the instant particle size of HA.

Liu teaches a mineralized collagen membrane for medical applications such as bone substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatite-like crystallites with a particular degree of crystallinity, habit and size (irregular platelike morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20. .

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Shirkanzadeh and Liu and utilize the instantly claimed calcium phosphates. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art wherein it is known to add the instantly claimed calcium phosphates with collagen.

Secondly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Shirkanzadeh, Liu, and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. It is noted that although Shirkanzadeh teaches the final coating comprises a network of crystals with a size of 2-5 microns, Shirkanzadeh does not teach away from using other particle sizes. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

Note that the process limitations in claims 11-19 are product-by-process limitation. According to the MPEP section 2113, "even though product by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production, if the product in the product-by-process claim is the same or obvious from a product of the prior art, the claim is

unpatentable even though the prior art was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed.Cir. 1985).

With regard to layers, collagen in combination with mineral components implicitly tends to separate phases or layers. US Patent 5,543,441 column 3 lines, 66 to column 4, line 5 is cited as art of interest to support examiner's argument.

Response to Arguments

Applicant argues that that "applicant's meaning of mineralize" is different and pertains to the field of bio-mineralization. Applicant argues that an inventor may be his or her own lexicographer. Applicant argues that Shirkanzadeh teaches a calcium phosphate layer that encourages adhesion of macromolecules such as collagen. Applicant argues this structure is too large to promote mineralization since Shirkanzadeh's crystal sizes are too large to promote mineralization. Applicant submits Figure 1, which shows the structure of Shirkanzadeh and submits Figure 3 as the instant invention wherein the crystal sizes are less than 1 micron.

Applicant's arguments filed 8/30/06 have been fully considered but they are not persuasive. The examiner notes that the applicant may be his or her own lexicographer however applicant has neither defined the term in the specification explicitly nor has the applicant pointed out where in the specification the term is defined. The examiners points to MPEP 2106 where it states "Any special meaning assigned to a term must be sufficiently clear in the specification that any departure from common usage would be so understood by a person of experience in the field of the invention." The applicant has not pointed to the page or pages in which the specification implicitly provides a definition of the term. Furthermore, the term "bone analogous coating" is also not defined. Therefore, the examiner is permitted the broadest reasonable interpretation.

Mineralize is defined by Merriam-Webster's Collegiate Dictionary as: "to impregnate or supply with mineral". Lastly, the examiner points out that both the prior art and the instant invention are in the same field of endeavor and thus applicant's argument that the instant invention is in the field of bio-mineralization is unclear.

It is noted that in the arguments of 12/21/04 and the arguments of 8/30/06, applicant states that the difference between the instant structure and Shirkanzadeh is the process of making the composition wherein the instant invention is "not just a simple mixture of calcium phosphate and collage". However, independent claim 1 does not recite any process steps, which provide this "unique structure". If applicant intends to demonstrate that the process provides a different product, it is not only applicant's burden to provide evidence substantiating this argument but also the independent claim must recite the process limitations.

The instant claims are directed to a product that requires amorphous calcium phosphate, hydroxyapatite with a size of 300-500nm, and collagen coated on a metallic implant. The only teaching lacking in Shirkanzadeh is the combination of amorphous calcium phosphate and hydroxyapatite, which is cured by Liu's teachings. The examiner points out that Shirkanzadeh teaches the use of calcium phosphate compounds in general (see column 3, line 21) and Liu teaches a that mixtures of calcium phosphates compounds are suitable for mineralized collagen matrices. The instant size is cured by Lussi et al. Although Shirkanzadeh teaches the network comprises particles crystals in the range of 2-5 microns, Shirkanzadeh does not teach away from using other particle sizes. Thus, a skilled artisan would have been motivated to use the instant size if one desired to produce a coating that was similar to bone.

Further, the applicant submitted a Figure on 12/21/04 that purportedly is a figure of the implant structure in US '921. However, the Figure is that of the implant disclosed by Shirkanzadeh in Materials Letters, volume 14. The applicant has not submitted the article for the examiner to determine if the Figure is indeed similar to that disclosed in US '941 and if the coating is prepared under similar conditions as described in US '941. If applicant wants this information to be considered, then applicant must submit the articles published by Shirkanzadeh in Materials Letters, volume 14. Further, the examiner cannot considered Lehninger "Principles of Biochemistry" since applicant has not submitted this article.

Claims 6 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shirkanzadeh (5,205,921) in view of Liu (6,300,315) in view of Lussi et al (5,167,961) in view of Sauk et al (4,780,450).

Shirkanzadeh discloses a method of depositing bioactive coatings on conductive substrates wherein a cathode and D.C. potential is applied to raise the interfacial pH at the cathode sufficiently enough to precipitate the desired oxide or phosphate thereon as a dense adherent film. See abstract. The substrate can be titanium alloy or steel and the coating is 50 microns thick for a uniform, continuous, and firmly bonded coating. See example 4. The coating composition includes calcium phosphate and non-toxic biological compounds, i.e. collagen. The inorganic compounds, i.e. calcium phosphate, may be co-precipitated with the organic compounds, i.e. collagen. This process allows the doping of specific ions in calcium phosphate crystals. See column 3, lines 5-20. Preferably crystalline calcium phosphate is utilized compared to amorphous calcium phosphate. The particle range of the calcium phosphate is 2-5 microns.

See example 2. The instant doping agents (carbonate and fluoride) are taught in the electrolyte solution.

The reference does not specify the instant collagen combination, i.e. type I and type III.

Sauk et al disclose a composition containing particulate calcium phosphate (hydroxyapatite) and type I collagen (col. 4, lines 59-66). A mixture of type I and type III collagen is taught (example 1). Sauk et al disclose in column 2, line 60 to column 3, line 5, "the composition preferably comprise a mixture of phosphophoryn calcium, a matrix material (type I collagen), and calcium phosphate ceramic. These compositions are intended to facilitate matrix-mediated mineralization, whereby the collagen defines a structural matrix and the salt regulates and directs mineral deposition in terms of its location, crystallinity and association with the calcium phosphate ceramic particles.

It would have been obvious for one of ordinary skill in the art at the time the invention was made to combine the teaching of Shirkanzadeh et al and Sauk et al and utilize a mixture of type I and type II collagen for the collagen matrix. One would have been motivated to do so since, as indicated by Sauk et al, this is a routine practice done at the time the invention was made.

Response to Arguments

Applicant argues that Sauk does not teach a porous composition comprising a crystalline calcium phosphate, a calcium salt, and collagen to osseous repair. Applicant argues that Sauk does not teach the instant coating process or teach electrochemical migration and precipitation.

Applicant's arguments filed 8/30/06 have been fully considered but they are not persuasive. It appears that applicant's arguments pertain to the references individually and not

the combination of references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner relies on Sauk to specifically teach the conventional use of a mixture of collagen types in collagen-calcium phosphate matrices. Applicant has not addressed the examiner's motivation and rather attacks for not teaching all of the claimed limitations. However, the combination of Shirkanzadeh, Liu, Lussi, and Sauk meet all the claimed limitations.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-5, 8, 10-16, 18-19, 21, 23-25, and 27 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of

U.S. Patent No. 6,524,718 in view of in view of Liu (6,300,315) in view of Lussi et al (5,167,961).

Claim 1 is directed to a coated metallic implant comprising a metallic implant and an outer layer, wherein the outer layer comprises a bone analogous coating comprising a collagen matrix mineralized with a calcium phosphate phase which is adhered to said implant surface, wherein the mineralized collagen matrix is constructed in the form of layers and each layer comprises a network of mineralized collagen fibrils, amorphous calcium phosphate clusters, and crystalline hydroxyapatite.

US patent is directed to a metallic object and a thin polyphase oxide coating, where said polyphase oxide coating is comprised of a first phase, wherein said first phase is a metal oxide phase, and a second phase, wherein said second phase is either an organic phase, an inorganic phase, or a combination of organic and inorganic phases, said polyphase oxide coating is produced by bringing the metallic substrate into contact with either an organic component, an inorganic component, or a combination of organic and inorganic components to be integrated into said polyphase oxide coating such that said second phase is present at or adjacent to the substrate surface and by simultaneously or subsequently anodically polarizing said substrate material in an electrolytic solution, wherein said metallic substrate is selected from the group consisting of aluminum, titanium, tantalum, zirconium, niobium, or their alloys, inclusive of intermetallic phases. Dependent claims are directed to the organic phases comprising collagen and the inorganic phases comprising calcium phosphate phases.

Liu teaches a mineralized collagen membrane for medical applications such as bone

substitutes. The mineralized collagen membrane comprises a substantially homogeneous mineralized collagen composite of about 30% to about 70% by weight of collagen component and about 30% to about 70% by weight of calcium phosphate minerals. The calcium phosphate minerals component is selected from tri-calcium phosphate, octa-calcium phosphate, amorphous calcium phosphate, hydroxyapatite, and mixture thereof. See column 3, lines 1-10 and column 5, lines 59-65. . The mineralized collagen provides mechanical properties superior compared to collagen alone. See column 3, lines 65-67. Liu teaches the membrane may also include antibiotics, bone growth factors, etc. See column 7, lines 45-50. Liu teaches the mineralized collagen membrane may include one or more additional components such as metals, such as alkali metals, other alkaline earth metals and the like. Liu teaches at lest a portion of the phosphate and/or hydroxyl content of the calcium- and phosphate-containing minerals may be replaced by a halogen, such as chloride or fluoride, carbonate and the like. See column 6, lines 1-20.

Lussi et al teach a process for preparing high purity bone mineral for implantation. See abstract. Lussi teaches natural bone mineral comprises hydroxyapatitelike crystallites with a particular degree of crystallinity, habit and size (irregular platelike morphology, 5-10nm in thickness 10-50 nm in length) and surface chemistry resulting from the calcium to phosphate ratio (37.5-38.0% calcium and 15.5-5-19.0% phosphorus). See column 1, lines 15-35. Lussi teaches prior art methods of making the bone mineral result in significant increase in crystal size which is much less readily remodelled on implantation since osteoclasts and osteoblasts cannot readily perform on such large crystals the dual function of mineral resorption and generation of new bone. Such implanted inserts may thus remain unchanged indefinitely eventually giving rise

to undesirable effects. Lussi teaches, alternatively, many synthetic tricalcium phosphate products tend to be resorbed too rapidly for osteoblasts to regenerate new bone. See column 1, lines 49-60. The process provides HA particles having a size from 20nm to 250; 100nm to 300nm; and 100nm to 400nm and a diameter of 34nm or 130 nm depending on the temperature used. See Table 1. Lussi teaches the HA particles have a similar structure to original bone. See column 4, lines 1-10. Lussi teaches it is important to avoid modification of the crystal sizes to ensure when the bone is implanted, it is readily converted into natural bone. See column 5, lines 18-30. The bone mineral according to the invention may thus be used as a remodelling implant or prosthetic bone replacement, for example in orthopedic surgery, including hip revisions, replacement of bone loss e.g. in traumatology, remodelling in maxillo facial surgery or filling periodontal defects and tooth extraction sockets. The bone mineral may also have adsorbed or absorbed therein one or more physiologically active substances including drugs or polypeptides, and proteins. See column 4, lines 30-60 and column 5, lines 10-20.

The difference between instant claims and US patent's claims is that the independent claim 1 requires specific calcium phosphates, i.e. hydroxyapatite and amorphous calcium phosphate. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made to utilize the instantly claimed calcium phosphates and arrive at the instantly claimed invention. One would have been motivated to do so since Liu teaches a mineralized collagen composition for medical applications wherein the calcium phosphate may be a mixture of different types of calcium phosphates including hydroxyapatite and amorphous calcium phosphate to provide a strong and flexible membrane. Thus, it would have been obvious to utilize the instantly clamed calcium phosphates since Liu demonstrates the state of the art

wherein it is known to add the instantly claimed calcium phosphates with collagen. Further, Worch teaches the combination of calcium phosphate phases and collagen wherein it is clear that Worch envisages utilizing more than one form of calcium phosphate in claim 4. Thus, the instantly claimed calcium phosphate types are considered an obvious modification. Note that the instant claims have comprising language and thus do not exclude the oxide coating. Note the instant claims are rejected over the process claims of US patent since one would necessarily have the coated metallic implant of the instant invention by the process of making and a restriction was not made in US '718. With regard to the instantly claimed doping agents, it would have been obvious to dope Worch's mineralized collagen since Liu teaches the adding minor portions of fluoride or carbonate to the mineralized collagen to provide certain desired properties and to resemble or simulate biological apatite.

With regard to the instantly claimed drugs, it would have been obvious to add certain drugs depending on the desired effect of the implant as taught by Liu.

Further, the instant claims differ from US patent claims in that they recite a specific HA size. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teaching of Rhee et al and Lussi et al and utilize the instant particle size. One would have been motivated to do so since Lussi teaches that HA particles with the instant particle size resorb better and cause generation of new bone faster. Further, Lussi teaches natural bone has the instant particle size. Thus, a skilled artisan would have been motivated to utilize the instant particle size since it closely resembles natural bone and allows for the body to convert the particles to natural bone faster.

Response to Arguments

Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

All the claims are rejected at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sharmila S. Gollamudi
Examiner
Art Unit 1616